CHARLES NICOLLE HOSPITAL - TUNIS, TUNISIA

Study Protocol

Individualized PEEP Based on Driving Pressure Versus Standard PEEP for Protective Ventilation in Upper Abdominal Surgery: A Randomized Controlled Trial

Driving Pressure-Guided Individualized PEEP versus Standard PEEP: Effects on Postoperative Pulmonary Complications in Upper Abdominal Digestive Surgery

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Ethics reference	ETHIQUE-HCN-117-2026
Principal investigator	Dr Hallouma Ben Fredj, MD
Lead organization	Charles Nicolle Hospital, Tunis, Tunisia
Study design	Prospective, randomized, controlled, parallel-group trial
Planned enrollment	210 participants

This document is a faithful English translation of the protocol approved by the Ethics Committee of Charles Nicolle Hospital. No substantive methodological changes have been introduced in the translation.

1 Study Design

This is a prospective, randomized, controlled, parallel-group study comparing two intraoperative ventilation strategies in adult patients undergoing upper abdominal digestive surgery. Participants and the postoperative outcome assessor will remain unaware of treatment allocation.

2 Study Objective

The primary objective is to compare a lung-protective ventilation strategy using standard positive end-expiratory pressure (PEEP) with a lung-protective ventilation strategy using PEEP individualized according to driving pressure, with respect to the occurrence of postoperative pulmonary complications during the first 7 days after upper abdominal digestive surgery.

3 Study Setting

The study will be conducted in the Visceral and Digestive Surgery Departments A and B at Charles Nicolle Hospital, Tunis, Tunisia.

4 Study Period

The planned study period is May 22, 2026 through June 1, 2027.

5 Study Population

5.1 Inclusion Criteria

Participants must meet all of the following criteria:

- Age 18 years or older.
- Scheduled for upper abdominal digestive surgery.
- Stable American Society of Anesthesiologists physical status I, II, or III.
- Moderate or high risk of postoperative pulmonary complications according to the ARISCAT score (ARISCAT score of at least 26).
- Written informed consent provided before enrollment.

5.2 Pre-randomization Exclusion Criteria

Patients meeting at least one of the following criteria will not be enrolled:

- Refusal to participate or absence of informed consent.
- Pregnancy.
- American Society of Anesthesiologists physical status greater than III.
- History of acute respiratory distress syndrome.
- Pulmonary arterial hypertension.
- Bronchopleural fistula.
- Chronic obstructive pulmonary disease with severe emphysema.
- Pre-existing cardiac arrhythmia.
- Decompensated heart failure.
- Known condition associated with increased intracranial pressure.
- Intra-abdominal hypertension.

5.3 Post-randomization Exclusion Criteria

Participants will be excluded after enrollment if any of the following occurs:

- Use of vasopressors at anesthetic induction.
- Intraoperative shock that prevents application of the ventilation protocol.
- Acute heart failure with right ventricular failure during surgery.
- Major non-adherence to the study protocol.

5.4 Sample Size Calculation

The primary endpoint is the incidence of postoperative pulmonary complications during the first 7 days after surgery. Based on published data in patients at moderate or high risk undergoing major abdominal surgery (ARISCAT score of at least 26), the baseline incidence of postoperative pulmonary complications with standard ventilation using PEEP of 5 cmH2O without recruitment is estimated at approximately 39%, particularly from the PROVHILO trial.

The study hypothesis is that protective ventilation with driving pressure-guided individualized PEEP and an alveolar recruitment maneuver will reduce this incidence to 20%. To detect an absolute difference of 19% with a two-sided alpha level of 5% and 80% statistical power, 95 participants are required per group. To account for an anticipated 10% rate of loss to follow-up, consent withdrawal, or unusable data, 210 participants will be randomized, with 105 participants in each study arm.

6 Outcome Measures

6.1 Primary Outcome Measure

The primary outcome is the occurrence of at least one postoperative pulmonary complication from the end of surgery through postoperative day 7. The composite includes:

- Postoperative pneumonia.
- Bronchospasm.
- Aspiration pneumonitis.
- Hypoxemia.
- Acute respiratory distress syndrome.
- Atelectasis.
- Pleural effusion.
- Pneumothorax.
- Radiographic pulmonary infiltrates.
- Extubation failure.
- Reintubation.
- Need for postoperative alveolar recruitment maneuvers.

Arterial blood gases will be obtained 10 minutes after tracheal intubation; 1, 2, and 3 hours after intubation; and at the end of surgery.

6.2 Secondary Outcome Measures

- Length of hospital stay.
- Postoperative admission to an intensive care unit.
- Intensive care unit length of stay.
- Intraoperative ventilatory parameters.
- Intraoperative hemodynamic parameters.
- Respiratory mechanics parameters.

7 Study Procedures

7.1 Preoperative Period

Each participant will undergo a preanesthetic assessment. The following information will be collected:

- Anthropometric data, including weight, height, and body mass index.
- Medical and surgical history.
- Smoking history.
- Anesthesia-focused clinical examination, including evaluation of the upper airway, signs of heart failure, venous access, and clinical hemostasis.

Preoperative laboratory tests will be requested according to the participant's history, clinical examination, and applicable recommendations. Preoperative fasting, the planned anesthetic technique, and the study protocol will be explained to each participant. Clear oral and written information will be provided, and written informed consent will be obtained before enrollment.

7.2 Randomization and Masking

Participants will be randomly assigned to one of two groups:

- Driving pressure-guided individualized PEEP group.
- Standard PEEP group.

Randomization will use a 1:1 allocation ratio and a computer-generated randomization list with variable-sized permuted blocks. Treatment allocation will be performed in real time in the operating room through a secure computerized system after final confirmation of eligibility.

Masking procedure. To reduce interpretation bias, the participant and the postoperative outcome assessor will remain unaware of treatment allocation.

- **Participant masking:** Participants will remain unaware of their assigned group because the intervention is delivered during general anesthesia.
- **Outcome assessor masking:** The physician assessing postoperative pulmonary complications through postoperative day 7 will be independent of the anesthesia team that managed the participant intraoperatively.
- **Operational safeguards:** The outcome assessor will not have access to the paper or electronic anesthesia record, intraoperative respiratory monitoring records describing PEEP levels, recruitment maneuvers, or driving pressure, or the randomization group. Allocation will be recorded in a dedicated research file separate from the clinical medical record used for postoperative surgical follow-up.

7.3 Intraoperative Period

7.3.1 Preparation Monitoring and Anesthetic Management

The operating room safety checklist will be systematically verified before anesthetic induction. Standard monitoring will include:

- Continuous electrocardiography.
- Heart rate.
- Noninvasive blood pressure.
- Pulse oxygen saturation.

Invasive arterial pressure monitoring will be used in participants considered more fragile at the discretion of the attending anesthesiologist. Three consecutive resting measurements of systolic, diastolic, and mean arterial pressure will be recorded before manipulation to establish preoperative

reference values. Two appropriately sized peripheral intravenous catheters will be inserted. Antibiotic prophylaxis or therapy will be administered according to applicable recommendations, ideally within 30 minutes before incision.

Preoxygenation will be performed for 3 minutes during spontaneous ventilation using a well-sealed face mask with an inspired oxygen fraction (FiO2) of 1.0, or by 8 vital-capacity breaths over 1 minute, until an end-expired oxygen fraction of at least 90% is achieved. Rapid-sequence anesthetic induction will use titrated intravenous propofol, with etomidate reserved for the most fragile participants, and succinylcholine. Fentanyl analgesia and additional neuromuscular blockade with cisatracurium will be administered as required.

After orotracheal intubation with a single-lumen tube, volume-controlled mechanical ventilation will be initiated. Ideal body weight will be calculated as follows:

- Women: 45.5 + 0.91 x [height in cm - 152.4].
- Men: 50 + 0.91 x [height in cm - 152.4].

Initial ventilator settings will be standardized as follows:

- FiO2 of 0.4.
- Tidal volume of 8 mL/kg ideal body weight.
- Inspiratory-to-expiratory ratio of 1:2.
- Respiratory rate adjusted between 12 and 20 breaths per minute to maintain end-tidal carbon dioxide between 35 and 45 mmHg.

Anesthesia will be maintained with a continuous propofol infusion using an electric syringe pump. Cisatracurium boluses will be administered as required to maintain deep neuromuscular blockade. Intraoperative targets will be a bispectral index of 40 to 60, mean arterial pressure of 60 to 90 mmHg, and deep neuromuscular blockade with a train-of-four count of zero and a post-tetanic count between 1 and 4.

7.3.2 PEEP Strategies

Three clinicians will participate in the intervention. Two trained and experienced investigators will perform alveolar recruitment maneuvers and PEEP titration according to the standardized procedure. A third clinician will collect intraoperative data and monitor protocol adherence.

Driving pressure-guided individualized PEEP group

After anesthetic induction, tracheal intubation, and initial hemodynamic stabilization, an alveolar recruitment maneuver will be followed by decremental PEEP titration.

Alveolar recruitment maneuver

The maneuver will be performed during pressure-controlled ventilation using:

- Inspiratory-to-expiratory ratio of 1:1.
- Respiratory rate of 15 breaths per minute.
- Initial PEEP of 5 cmH2O.

PEEP will be increased in 5 cmH2O increments until a recruitment inspiratory pressure of 40 cmH2O is reached and maintained for 15 respiratory cycles. The maneuver will be stopped if hemodynamic instability or ventilatory intolerance occurs.

Decremental PEEP titration

Immediately after the recruitment maneuver, decremental PEEP titration will be performed with the following standardized settings:

- Volume-controlled ventilation.

- Tidal volume of 8 mL/kg ideal body weight.
- Respiratory rate of 12 breaths per minute.
- Inspiratory-to-expiratory ratio of 1:2.
- Inspiratory pause of 30%.

PEEP will initially be set at 10 cmH2O and then reduced in 1 cmH2O increments to 4 cmH2O. At each PEEP level, after equilibration for 10 respiratory cycles, plateau pressure will be measured statically using a 2- to 3-second end-inspiratory occlusion. Driving pressure will be calculated as plateau pressure minus PEEP.

The individualized PEEP selected for each participant will be the level associated with the lowest driving pressure during titration. If several PEEP levels produce the same minimum driving pressure, the lowest PEEP level will be selected. The selected PEEP will then be maintained throughout surgery.

Repeat PEEP titration

A new recruitment maneuver followed by repeat PEEP titration will be performed after an event likely to cause alveolar derecruitment, including:

- Placement of surgical retractors.
- Insufflation or desufflation of the pneumoperitoneum.
- Disconnection of the breathing circuit.
- Tracheal suctioning.
- Major change in surgical position.

Retitration will be undertaken only after adequate neuromuscular blockade has been restored and hemodynamic stability has been confirmed.

Standard PEEP group

In the standard PEEP group, PEEP will be set at 5 cmH2O when mechanical ventilation begins and maintained at this level throughout surgery unless a rescue intervention is required.

7.3.3 Intraoperative Rescue Measures

If intraoperative desaturation occurs, defined as SpO2 below 95%, standardized management will include:

- Increasing the inspired oxygen fraction.
- Confirming the position of the tracheal tube.
- Confirming patency of the breathing circuit.
- Performing an alveolar recruitment maneuver.
- Temporarily increasing PEEP at the discretion of the attending anesthesiologist.

If desaturation persists despite an FiO2 of 1.0, PEEP may be further increased in 2 cmH2O increments. If hemodynamic instability occurs, ventilator settings may be adapted by the anesthesiologist and vasopressor treatment administered as required. Arterial hypotension is defined as systolic arterial pressure below 90 mmHg or a decrease greater than 20% from the preoperative value.

7.3.4 Ventilatory and Hemodynamic Data

The following parameters will be recorded 10 minutes after tracheal intubation; 1, 2, and 3 hours after intubation; and at the end of surgery:

- Tidal volume.
- PEEP.
- Peak airway pressure.

- Plateau pressure.
- Driving pressure.
- Static compliance.
- Dynamic compliance.
- Arterial pressure.
- Heart rate.

The following formulas will be used:

- Driving pressure = plateau pressure - PEEP.
- Static compliance = tidal volume / (plateau pressure - PEEP).
- Dynamic compliance = tidal volume / (peak airway pressure - PEEP).

7.3.5 Postanesthesia Care Unit

Standardized respiratory, hemodynamic, and neurological monitoring will be provided in the postanesthesia care unit. Arterial blood gas analysis may be performed according to the participant's clinical status. If SpO2 is below 92%, oxygen will be administered through nasal cannulae or a face mask.

7.4 Postoperative Period

7.4.1 Immediate Postoperative Period

After surgery, participants will be monitored in the postanesthesia care unit. Hemodynamic, respiratory, and neurological status will be monitored according to current unit protocols.

7.4.2 Standardized Postoperative Care

Postoperative monitoring will cover vital signs, bleeding, the operative wound, and return of bowel function. Postoperative prescriptions will follow the department protocol. All participants will receive:

- Early respiratory physiotherapy.
- Multimodal analgesia targeting a visual analog pain score below 3.
- Antibiotic prophylaxis when indicated.
- Preventive anticoagulation when indicated.
- Acid suppression with a proton pump inhibitor.
- Appropriate fluid and electrolyte therapy.

A reference chest radiograph will be obtained routinely on postoperative day 1.

8 Data Collection

Data collected during the preoperative, intraoperative, and postoperative periods will be recorded on a standardized case report form. Anthropometric and demographic data will include height, weight, age, smoking status, and medical and surgical history. The type and indication of surgery will be documented. Operative characteristics, including incision time and the time surgery ends, will be recorded.

Hemodynamic data will include systolic, diastolic, and mean arterial pressure and heart rate, measured every 5 minutes until the end of surgery. Intravenous fluid volume, blood loss, and intraoperative urine output will be recorded. The number of recruitment maneuvers and ventilatory parameters, including PEEP and tidal volume, will be entered on the data collection form.

The following summary measures will be derived from predefined intraoperative measurements:

- Median intraoperative driving pressure, calculated as plateau pressure measured at the end of an inspiratory pause minus PEEP.
- Respiratory system compliance, calculated as tidal volume divided by driving pressure.

- Median intraoperative PEEP.

Arterial blood gases will be obtained 10 minutes after tracheal intubation; 1, 2, and 3 hours after intubation; and at the end of surgery. Intraoperative adverse events, including tachycardia, hypertension, hypotension, and bradycardia, will be monitored and recorded. Postoperative pulmonary complications will be assessed during the first 2 postoperative days and then through postoperative day 7.

9 Ethical Considerations

The study will be conducted after participants receive clear oral and written information and provide written informed consent for participation and use of the collected data. Refusal to participate will result in non-enrollment. Confidentiality will be maintained through anonymized data collection and strictly scientific use of the information. No conflict of interest is declared for this study. Access to study data will be restricted to authorized investigators. Data will be retained for 5 years after study completion or the last publication, whichever is later.

10 Statistical Analysis

Data entry and analysis will be performed using appropriate statistical software.

10.1 Descriptive Analysis

Normally distributed continuous variables will be summarized as mean and standard deviation. Non-normally distributed continuous variables will be summarized as median and interquartile range. Categorical variables will be summarized as counts and percentages.

10.2 Analytical Methods

Associations between two categorical variables will be analyzed using Pearson's chi-square test when its assumptions are met; otherwise, Fisher's exact test will be used. Associations between a categorical variable and a quantitative variable will be analyzed using Student's t-test for comparison of two means when the quantitative variable is normally distributed; otherwise, the nonparametric Mann-Whitney test will be used. Statistical significance will be set at 0.05. In multivariable analysis, associations will be expressed as odds ratios with 95% confidence intervals.